

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 December 2003 (04.12.2003)

PCT

(10) International Publication Number
WO 03/099827 A1

- (51) International Patent Classification⁷: **C07D 513/04, A61K 31/55, A61P 35/00**
- (21) International Application Number: **PCT/HR03/00023**
- (22) International Filing Date: **20 May 2003 (20.05.2003)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
P20020451A 23 May 2002 (23.05.2002) HR
- (71) Applicant (for all designated States except US): **PLIVA d.d. [HR/HR]; Ulica grada Vukovara 49, HR-10000 Zagreb, HRVATSKA (HR).**
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **MERCEP, MLADEN [HR/HR]; Majstora Radonje 10, HR-10 000 Zagreb (HR). MESIC, Milan [HR/HR]; Slavonskog 8, HR-10 000 Zagreb (HR). MODRIC, Marina [HR/HR]; Mirna 24, HR-10 000 Zagreb (HR). PESIC, Dijana [HR/HR]; Prokljanska 18, HR-22 000 Sibenik (HR). KIDEMET, Davor [HR/HR]; Krizaniceva 55, HR-42 000 Varazdin (HR).**
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/099827 A1

(54) Title: **1-THIA-3-AZA-DIBENZOAZULENES AS INHIBITORS OF TUMOUR NECROSIS FACTOR PRODUCTION AND INTERMEDIATES FOR THE PREPARATION THEREOF**

(57) Abstract: The present invention relates to derivatives of 1-thia-3-aza-dibenzoazulene class, to their pharmacologically acceptable salts and solvates, to processes and intermediates for the preparation thereof as well as to their antiinflammatory effects, especially to the inhibition of tumour necrosis factor- α (TNF- α) production and the inhibition of interleukin-1 (IL-1) production as well as to their analgetic action.

**1-THIA-3-AZA-DIBENZOAZULENES AS INHIBITORS OF
TUMOUR NECROSIS FACTOR PRODUCTION AND
INTERMEDIATES FOR THE PREPARATION THEREOF**

Technical Field

The present invention relates to 1-thia-3-aza-dibenzoazulene derivatives, to their pharmacologically acceptable salts and solvates, to processes and intermediates for the preparation thereof as well as to their antiinflammatory effects, especially to the inhibition of tumour necrosis factor- α (TNF- α) production and the inhibition of interleukin-1 (IL-1) production as well as to their analgetic action.

Prior Art

Some 1,3-diaza-dibenzoazulene derivatives and salts thereof are known as a novel class of compounds having an antiinflammatory action (US 3,711,489, US 4,198,421 and CA 967,573). From the class of 1-thia-dibenzoazulenes, in the literature there are described derivatives substituted in 2-position with methyl, methyl-ketone, nitro group or with carboxylic group derivatives (Cagniant PG, *C. R. Hebd. Seances Acad. Sci.*, 1976, 283:683-686) and 1-thia-dibenzoazulene derivatives having alkyloxy substituents in 2-position (WO 01/878990), which also possess strong antiinflammatory action.

According to our knowledge and to available literature data, derivatives of 1,8-dithia-3-aza-dibenzoazulenes having in 2-position an amino group are well-known (Kovtunenkov VA et al., *Ukr. Khim. Zh.*, 1983 43:975-978), whereas other derivatives and especially those having alkyl or some other groups, which are alkyl derivatives and intermediates for the preparation thereof, in 2-position have now been prepared and described for the first time. It has not been known either that dibenzoazulenes

from the class of thiazoles show antiinflammatory action (inhibitors of TNF- α production, inhibitors of IL-1 production) and/or analgetic action.

TNF- α is defined as a serum factor induced by endotoxin and causing tumour necrosis *in vitro* and *in vivo* (Carswell EA et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1975, 72:3666-3670). Besides an antitumour action, TNF- α also possesses numerous other biological actions important in the homeostasis of an organism and in pathophysiological conditions. The main sources of TNF- α are monocytes-macrophages, T-lymphocytes and mastocytes.

The discovery that anti-TNF- α antibodies (cA2) have an action in treating patients with rheumatoid arthritis (RA) (Elliott M et al., *Lancet*, 1994, 344:1105-1110) led to an increased interest in finding novel TNF- α production inhibitors as possible potent drugs for RA. Rheumatoid arthritis is an autoimmune chronic inflammatory disease characterized by irreversible pathological changes in the joints. Besides in RA, TNF- α antagonists may also be used in numerous pathological conditions and diseases such as spondylitis, osteoarthritis, gout and other arthritic conditions, sepsis, septic shock, toxic shock syndrom, atopic dermatitis, contact dermatitis, psoriasis, glomerulonephritis, lupus erythematosus, scleroderma, asthma, cachexia, chronic obstructive lung disease, congestive cardiac arrest, insulin resistance, lung fibrosis, multiple sclerosis, Crohn's disease, ulcerative colitis, viral infections and AIDS.

Some of the proofs indicating the biological importance of TNF- α were obtained by *in vivo* experiments in mice, in which mice gens for TNF- α or its receptor were inactivated. Such animals are resistant to collagen-induced arthritis (Mori L et al., *J. Immunol.*, 1996, 157:3178-3182) and to endotoxin-caused shock (Pfeffer K et al., *Cell*, 1993, 73:457-467). In animal experiments where TNF- α level was increased, a chronic inflammatory polyarthritis similar to RA occurred (Georgopoulos S et al., *J.Inflamm.*, 1996, 46:86-97; Keffer J et al., *EMBO J.*, 1991, 10:4025-4031) and its

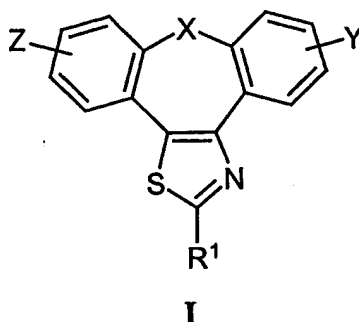
clinical picture was alleviated by inhibitors of TNF- α production. The treatment of such inflammatory and pathological conditions usually includes the application of non-steroid antiinflammatory drugs and, in more severe cases, gold salts, D-penicillinamine or methotrexate are administered. Said drugs act symptomatically, but they do not stop the pathological process. Novel approaches in the therapy of rheumatoid arthritis are based upon drugs such as tenidap, leflunomide, cyclosporin, FK-506 and upon biomolecules neutralizing the TNF- α action. At present there are commercially available etanercept (Enbrel, Immunex/Wyeth), a fusion protein of the soluble TNF- α receptor, and infliximab (Remicade, Centocor), a chimeric monoclonal human and mouse antibody. Besides in RA therapy, etanercept and infliximab are also registered for the therapy of Crohn's disease (*Exp. Opin. Invest. Drugs*, 2000, 9:103).

In an optimal RA therapy, besides inhibition of TNF- α secretion, also the inhibition of IL-1 production is very important since IL-1 is an important cytokin in cell regulation and immunoregulation as well as in pathophysiological conditions such as inflammation (Dinarello CA et al., *Rev. Infect. Disease*, 1984, 6:51). Well-known biological activities of IL-1 are: activation of T-cells, induction of elevated temperature, stimulation of secretion of prostaglandine or collagenase, chemotaxia of neutrophils and reduction of iron level in plasma (Dinarello CA, *J. Clinical Immunology*, 1985, 5:287). Two receptors to which IL-1 may bind are well-known: IL-1RI and IL-1RII. IL-1RI transfers a signal intracellularly, whereas IL-1RII, though situated on the cell surface, does not transfer a signal inside the cell. Since IL-1RII binds IL-1 as well as IL-1RI, it may act as a negative regulator of IL-1 action. Besides this mechanism of signal transfer regulation, another natural antagonist of IL-1 receptor (IL-1ra) is present in cells. This protein binds to IL-1RI but does not bring about a stimulation thereof. The potency of IL-1ra in stopping the signal transfer stimulated by IL-1 is not high and its concentration has to be 500 times higher than that of IL-1 in order to achieve a break in the signal transfer. Recombinant human IL-1ra (Amgen) was clinically tested (Bresnihan B et al., *Arthrit. Rheum.*, 1996, 39:73) and the obtained results indicated an improvement of the clinical picture in RA

patients over a placebo. These results indicate the importance of the inhibition of IL-1 action in treating diseases such as RA where IL-1 production is disturbed. Since there exists a synergistic action of TNF- α and IL-1, dual TNF- α and IL-1 inhibitors may be used in treating conditions and diseases related to an enhanced production of TNF- α and IL-1.

Solution of Technical Problem

The present invention relates to 1-thia-3-aza-dibenzoazulenes of the formula I



wherein

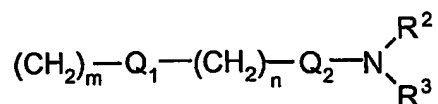
X may be CH₂ or a hetero atom such as O, S, S(=O), S(=O)₂, or NR^a, wherein R^a is hydrogen or a protecting group;

Y and Z independently from each other denote one or more identical or different substituents linked to any available carbon atom, and may be halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo-C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, trifluoromethoxy, C₁-C₄ alkanoyl, amino, amino-C₁-C₄ alkyl, N-(C₁-C₄-alkyl)amino, N,N-di(C₁-C₄-alkyl)amino, thiol, C₁-C₄ alkylthio, sulfonyl, C₁-C₄ alkylsulfonyl, sulfinyl, C₁-C₄ alkylsulfinyl, carboxy, C₁-C₄ alkoxycarbonyl, cyano, nitro;

R¹ may be hydrogen, halogen, an optionally substituted C₁-C₇ alkyl or C₂-C₇ alkenyl, C₂-C₇ alkynyl, an optionally substituted aryl or heteroaryl and a

heterocycle, hydroxy, hydroxy-C₂-C₇ alkenyl, hydroxy-C₂-C₇ alkynyl, C₁-C₇ alkoxy, thiol, thio-C₂-C₇ alkenyl, thio-C₂-C₇ alkynyl, C₁-C₇ alkylthio, amino-C₂-C₇ alkenyl, amino-C₂-C₇ alkynyl, amino-C₁-C₇ alkoxy, C₁-C₇ alkanoyl, aroyl, oxo-C₁-C₇ alkyl, C₁-C₇ alkanoyloxy, carboxy, an optionally substituted (C₁-C₇ alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C₁-C₇-alkyl)carbamoyl, *N,N*-di(C₁-C₇-alkyl)carbamoyl, cyano, cyano-C₁-C₇ alkyl, sulfonyl, C₁-C₇ alkylsulfonyl, sulfinyl, C₁-C₇ alkylsulfinyl, nitro,

or a substituent of the formula II



II

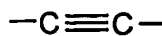
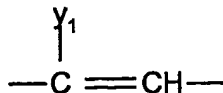
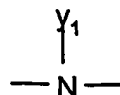
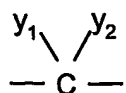
wherein

R² and R³ simultaneously or independently from each other may be hydrogen, C₁-C₄ alkyl, aryl or together with N have the meaning of an optionally substituted heterocycle or heteroaryl;

m represents an integer from 1 to 3;

n represents an integer from 0 to 3;

Q₁ and Q₂ represent, independently from each other, oxygen, sulfur or groups:



wherein the substituents

y_1 and y_2 independently from each other may be hydrogen, halogen, an optionally substituted C_1 - C_4 alkyl or aryl, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 alkanoyl, thiol, C_1 - C_4 alkylthio, sulfonyl, C_1 - C_4 alkylsulfonyl, sulfinyl, C_1 - C_4 alkylsulfinyl, cyano, nitro or together form a carbonyl or imino group;

as well as to pharmacologically acceptable salts and solvates thereof.

The term "halo", "hal" or "halogen" relates to a halogen atom which may be fluorine, chlorine, bromine or iodine.

The term "alkyl" relates to alkyl groups with the meaning of alkanes wherefrom radicals are derived, which radicals may be straight, branched or cyclic or a combination of straight and cyclic ones and branched and cyclic ones. The preferred straight or branched alkyls are e.g. methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl and *tert*-butyl. The preferred cyclic alkyls are e.g. cyclopentyl or cyclohexyl.

The term "haloalkyl" relates to alkyl groups which must be substituted with at least one halogen atom. The most frequent haloalkyls are e.g. chloromethyl, dichloromethyl, trifluoromethyl or 1,2-dichloropropyl.

The term "alkenyl" relates to alkenyl groups having the meaning of hydrocarbon radicals, which may be straight, branched or cyclic or are a combination of straight and cyclic ones or branched and cyclic ones, but having at least one carbon-carbon double bond. The most frequent alkenyls are ethenyl, propenyl, butenyl or cyclohexenyl.

The term "alkinyl" relates to alkinyl groups having the meaning of hydrocarbon radicals, which are straight or branched and contain at least one and at most two carbon-carbon triple bonds. The most frequent alkinyls are e.g. ethinyl, propinyl or butinyl.

The term "alkoxy" relates to straight or branched chains of alkoxy group. Examples of such groups are methoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

The term "aryl" relates to groups having the meaning of an aromatic ring, e.g. phenyl, as well as to fused aromatic rings. Aryl contains one ring with at least 6 carbon atoms or two rings with totally 10 carbon atoms and with alternating double (resonant) bonds between carbon atoms. The most frequently used aryls are e.g. phenyl or naphthyl. In general, aryl groups may be linked to the rest of the molecule by any available carbon atom via a direct bond or via a C₁-C₄ alkylene group such as methylene or ethylene.

The term "heteroaryl" relates to groups having the meaning of aromatic and partially aromatic groups of a monocyclic or bicyclic ring with 4 to 12 atoms, at least one of them being a hetero atom such as O, S or N, and the available nitrogen atom or carbon atom is the binding site of the group to the rest of the molecule either via a direct bond or via a C₁-C₄ alkylene group defined earlier. Examples of this type are thiophenyl, pyrrolyl, imidazolyl, pyridinyl, oxazolyl, thiazolyl, pyrazolyl, tetrazolyl, pirimidinyl, pyrazinyl, quinolinyl or triazinyl.

The term "heterocycle" relates to five-member or six-member, fully saturated or partly unsaturated heterocyclic groups containing at least one hetero atom such as O, S or N, and the available nitrogen atom or carbon atom is the binding site of the group to the rest of the molecule either via a direct bond or via a C₁-C₄ alkylene group defined

earlier. The most frequent examples are morpholinyl, piperidyl, piperazinyl, pyrrolidinyl, pirazinyl or imidazolyl.

The term "alkanoyl" group relates to straight chains of acyl group such as formyl, acetyl or propanoyl.

The term "aroyl" group relates to aromatic acyl groups such as benzoyl.

The term "optionally substituted alkyl" relates to alkyl groups which may be optionally additionally substituted with one, two, three or more substituents. Such substituents may be halogen atom (preferably fluorine or chlorine), hydroxy, C₁-C₄ alkoxy (preferably methoxy or ethoxy), thiol, C₁-C₄ alkylthio (preferably methylthio or ethylthio), amino, *N*-(C₁-C₄) alkylamino (preferably *N*-methylamino or *N*-ethylamino), *N,N*-di(C₁-C₄-alkyl)-amino (preferably dimethylamino or diethylamino), sulfonyl, C₁-C₄ alkylsulfonyl (preferably methylsulfonyl or ethylsulfonyl), sulfinyl, C₁-C₄ alkylsulfinyl (preferably methylsulfinyl).

The term "optionally substituted alkenyl" relates to alkenyl groups optionally additionally substituted with one, two or three halogen atoms. Such substituents may be e.g. 2-chloroethenyl, 1,2-dichloroethenyl or 2-bromo-propene-1-yl.

The term "optionally substituted aryl, heteroaryl or heterocycle" relates to aryl, heteroaryl and heterocyclic groups which may be optionally additionally substituted with one or two substituents. The substituents may be halogen (preferably chlorine or fluorine), C₁-C₄ alkyl (preferably methyl, ethyl or isopropyl), cyano, nitro, hydroxy, C₁-C₄ alkoxy (preferably methoxy or ethoxy), thiol, C₁-C₄ alkylthio (preferably methylthio or ethylthio), amino, *N*-(C₁-C₄) alkylamino (preferably *N*-methylamino or *N*-ethylamino), *N,N*-di(C₁-C₄-alkyl)-amino (preferably *N,N*-dimethylamino or *N,N*-diethylamino), sulfonyl, C₁-C₄ alkylsulfonyl (preferably methylsulfonyl or ethylsulfonyl), sulfinyl, C₁-C₄ alkylsulfinyl (preferably methylsulfinyl).

When X has the meaning of NR^a and R^a has the meaning of a protecting group, then R^a relates to groups such as alkyl (preferably methyl or ethyl), alkanoyl (preferably acetyl), alkoxy carbonyl (preferably methoxycarbonyl or *tert*-butoxycarbonyl), arylmethoxycarbonyl (preferably benzyloxycarbonyl), aroyl (preferably benzoyl), arylalkyl (preferably benzyl), alkylsilyl (preferably trimethylsilyl) or alkylsilylalkoxyalkyl (preferably trimethylsilylethoxymethyl).

When R^2 and R^3 together with N have the meaning of heteroaryl or heterocycle, this means that such heteroaryls or heterocycles have at least one carbon atom replaced by a nitrogen atom, through which the groups are linked to the rest of the molecule. Examples of such groups are morpholine-4-yl, piperidine-1-yl, pyrrolidine-1-yl, imidazole-1-yl or piperazine-1-yl.

The term "pharmaceutically suitable salts" relates to salts of the compounds of the formula I and include e.g. salts with C_1 - C_4 alkylhalides (preferably methyl bromide, methyl chloride) (quaternary ammonium salts), with inorganic acids (hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric or sulfuric acids) or with organic acids (tartaric, acetic, citric, maleic, lactic, fumaric, benzoic, succinic, methane sulfonic or *p*-toluene sulfonic acids).

Some compounds of the formula I may form salts with organic or inorganic acids or bases and these are also included in the present invention.

Solvates (most frequently hydrates) which may be formed by the compounds of the formula I or salts thereof are also an object of the present invention.

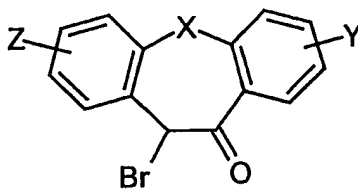
Depending upon the nature of particular substituents, the compounds of the formula I may have geometric isomers and one or more chiral centres so that there can exist

enantiomers or diastereoisomers. The present invention also relates to such isomers and mixtures thereof, including racemates.

The present invention also relates to all possible tautomeric forms of particular compounds of the formula I.

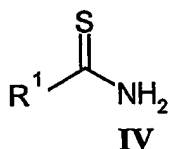
A further object of the present invention relates to the preparation of compounds of the formula I according to processes comprising:

- a) a cyclization of α -bromoketones of the formula III:



III

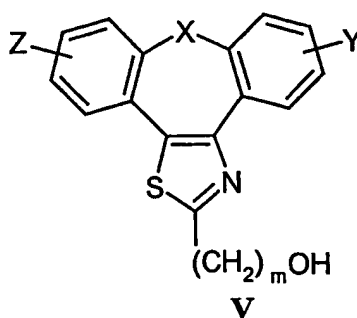
with the compounds of the formula IV:



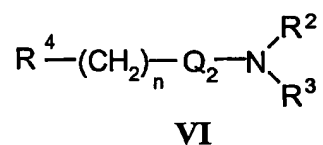
IV

- b) for the compounds of the formula I, wherein Q₁ has the meaning of -O-,
a reaction of alcohols of the formula V:

11



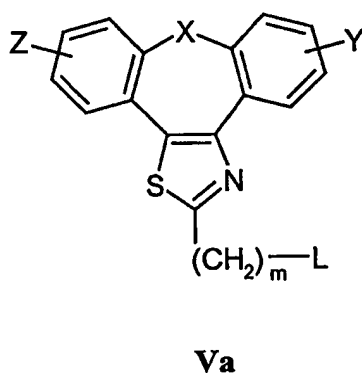
with the compounds of the formula VI:



wherein R^4 has the meaning of a leaving group;

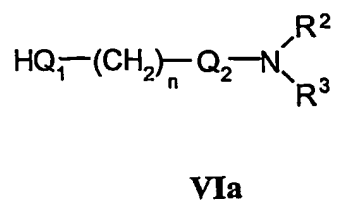
- c) for the compounds of the formula I, wherein Q_1 has the meaning of -O-, -NH-, -S- or -C≡C-,

a reaction of the compounds of the formula Va:



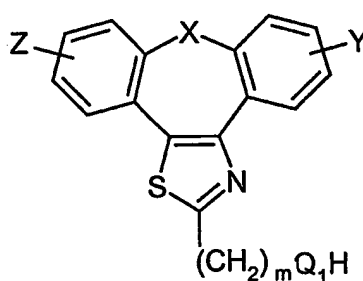
wherein L has a meaning of a leaving group,

with the compounds of the formula VIa:



- d) for the compounds of the formula **I**, wherein Q_1 has the meaning of a heteroatom
-O-, -NH- ili -S-,

a reaction of the compounds of the formula **Vb**:



Vb

with the compounds of the formula **VI**, wherein R^4 has the meaning of a leaving group;

- e) for the compounds of the formula **I**, wherein Q_1 has the meaning of $-C=C-$,
a reaction of the compounds of the formula **Va**, wherein Q_1 has the meaning of carbonyl, with phosphorous ylides.

Preparation methods:

- a) Cyclization of α -bromoketones of the formula **III** and thioamides of the formula **IV** is carried out by methods disclosed for the preparation of analogous compounds (Teitei, *Aust. J. Chem.*, 1980, 33:605-611). The reaction is carried out in an appropriate solvent such as e.g. ethanol, propanol, isopropanol, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, toluene or xylene at an elevated temperature (preferably from 50°C to 150°C). The formed tetracyclic products may be isolated by column chromatography or recrystallization from an appropriate solvent.

The starting compounds for this reaction are already known or they are prepared by methods described for the preparation of analogous compounds: for α -bromoketones of the formula III in e.g. US 3,711,489 or US 4,198,421, or for thioamides of the formula IV, in e.g. Kavtunen V.A. et al., *Ukr. Khim. Zh.*, 1983, 49:975-978. The so obtained compounds may be purified, isolated and characterized or may be subjected to a further cyclisation reaction without isolation.

b) The compounds of the formula I according to the present process may be prepared by a reaction of alcohols of the formula V and of compounds of the formula VI, wherein R^4 has the meaning of a leaving group, which may be a halogen atom (most frequently bromine, iodine or chlorine) or sulfonyloxy group (most frequently trifluoromethylsulfonyloxy or *p*-toluenesulfonyloxy). The condensation reaction may be carried out according to methods disclosed for the preparation of analogous compounds (Menozzi G et al., *J. Heterocyclic Chem.*, 1997, 34:963-968 or WO 01/87890). The reaction is carried out at a temperature from 20°C to 100°C during 1 to 24 hours in a two-phase system (preferably with 50% NaOH/toluene) in the presence of a phase transfer catalyst (preferably benzyl triethyl ammonium chloride, benzyl triethyl ammonium bromide, cetyl trimethyl bromide). After the treatment of the reaction mixture, the products formed are isolated by recrystallization or chromatography on a silica gel column.

The starting compounds, alcohols of the formula V, may be prepared from the compounds of the formula I, wherein R^1 has the meaning of an appropriate functional group. So, the alcohols of the formula V may be obtained by the reduction of an alkanoyl group (e.g. formyl) or alkyloxycarbonyl group (e.g. methyloxycarbonyl or ethyloxycarbonyl) by the use of metal hydrides such as lithium aluminum hydride or sodium borohydride. Further, the alcohols of the formula IV may be prepared by hydrolysis of the corresponding esters (in alkaline or acidic mediums).

The starting compounds of the formula VI are already known or are prepared according to methods disclosed for the preparation of analogous compounds.

c) Compounds of the formula I may be prepared according to the present process by reacting compounds of the formula Va, wherein L has the meaning of a leaving group as defined earlier for R^4 , and compounds of the formula VIa, wherein Q_1 has the meaning of oxygen, nitrogen, sulfur or $-C\equiv C-$. The most suitable condensation reactions are reactions of nucleophilic substitution on a saturated carbon atom as disclosed in the literature.

The starting compounds of the formula Va (most frequently halides) may be obtained by halogenation (e.g. bromination or chlorination) of compounds of the formula V with the usual halogenating agents (e.g. hydrobromic acid, PBr_3 , $SOCl_2$ or PCl_5) by processes as disclosed in the literature. The obtained compounds may be isolated or may be used without isolation as suitable intermediates for the preparation of the compounds of the formula I.

The starting compounds of the formula VIa are already known or are prepared according to methods disclosed for the preparation of analogous compounds.

d) The compounds of the formula I, wherein Q_1 has the meaning of $-O-$, $-NH-$ or $-S-$, may be prepared by the condensation of the compounds of the formula Vb and of compounds of the formula VI, wherein R^4 has the meaning of a leaving group as defined earlier. The reaction may be carried out at reaction conditions disclosed in the method b) or at conditions of the nucleophilic substitution reactions disclosed in the literature. The starting alcohols, amines or thiols may be obtained by a reaction of water, ammonia or hydrogen sulfide with compounds Va according to processes disclosed in the literature.

e) The alcohols of the structure V may be oxidized to corresponding compounds of the formula Vb, wherein Q_1 has the meaning of carbonyl, which may further, by reaction with corresponding ylide reagents, result in a prolongation of the chain and in the formation of an alkenyl substituent with carbonyl or ester groups as disclosed in HR patent application No. 20000310.

Besides the above-mentioned reactions, the compounds of the formula I may be prepared by transforming other compounds of the formula I and it is to be understood that the present invention also comprises such compounds and processes. A special example of a change of a functional group is the reaction of the aldehyde group with chosen phosphorous ylides resulting in a prolongation of the chain and the formation of an alkenyl substituent with carbonyl or ester groups as disclosed in HR patent application No. 20000310. These reactions are carried out in solvents such as benzene, toluene or hexane at elevated temperature (most frequently at boiling temperature).

By reacting the compounds of the formula Va with 1-alkyne in an alkaline medium (such as sodium amide in ammonia), compounds of the formula I, wherein Q_1 is $-C\equiv C-$, are obtained. The reaction conditions of this process are disclosed in the literature. At similar reaction conditions (nucleophilic substitution) various ether, thioether or amine derivatives may be prepared.

The formylation of the compounds of the formula I by processes such as e.g. Vilsmeier acylation or reaction of *n*-BuLi and *N,N*-dimethylformamide is a further general example of a transformation. The reaction conditions of these processes are well-known in the literature.

By hydrolysis of the compounds of the formula I having nitrile, amide or ester groups, there may be prepared compounds with a carboxyl group, which are suitable

intermediates for the preparation of other compounds with novel functional groups such as e.g. esters, amides, halides, anhydrides, alcohols or amines.

Oxidation or reduction reactions are a further possibility of the change of substituents in the compounds of the formula I. The most frequently used oxidation agents are peroxides (hydrogen peroxide, *m*-chloroperbenzoic acid or benzoyl peroxide) or permanganate, chromate or perchlorate ions. Thus e.g. by the oxidation of an alcohol group by pyridinyl dichromate or pyridinyl chlorochromate, an aldehyde group is formed, which group may be converted to a carboxyl group by further oxidation. By oxidation of the compounds of the formula I, wherein R¹ has the meaning of alkyl, with lead tetraacetate in acetic acid or with *N*-bromosuccinimide using a catalytic amount of benzoyl peroxide, a corresponding carbonyl derivative is obtained.

By a selective oxidation of alkylthio group, alkylsulfinyl or alkylsulfonyl groups may be prepared.

By the reduction of the compounds with a nitro group, the preparation of amino compounds is made possible. The reaction is carried out under usual conditions of catalytic hydrogenation or electrochemically. By catalytic hydrogenation using palladium on carbon, alkenyl substituents may be converted to alkyl ones or the nitrile group can be converted to aminoalkyl.

Various substituents of the aromatic structure in the compounds of the formula I may be introduced by standard substitution reactions or by usual changes of individual functional groups. Examples of such reactions are aromatic substitutions, alkylations, halogenation, hydroxylation as well as oxidation or reduction of substituents. Reagents and reaction conditions are known from the literature. Thus e.g. by aromatic substitution a nitro group is introduced in the presence of concentrated nitric acid and sulfuric acid. By using acyl halides or alkyl halides, the introduction of an acyl group or an alkyl group is made possible. The reaction is carried out in the presence of

Lewis acids such as aluminum- or iron-trichloride in conditions of Friedel-Crafts reaction. By the reduction of the nitro group, an amino group is obtained, which is by a diazotizing reaction converted to a suitable starting group, which may be replaced with one of the following groups: H, CN, OH, Hal.

In order to prevent undesired interaction in chemical reactions, it is often necessary to protect certain groups such as e.g. hydroxy, amino, thio or carboxy. For this purpose a great number of protecting groups may be used [Green TW, Wuts PGH, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999] and the choice, use and elimination thereof are conventional methods in chemical synthesis.

A convenient protection for amino or alkylamino groups are groups such as e.g. alkanoyl (acetyl), alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl); arylmethoxycarbonyl (benzyloxycarbonyl), aroyl (benzoyl) or alkylsilyl (trimethylsilyl or trimethylsilylethoxymethyl) groups. The conditions of removing a protecting group depend upon the choice and the characteristics of this group. Thus e.g. acyl groups such as alkanoyl, alkoxycarbonyl or aroyl may be eliminated by hydrolysis in the presence of a base (sodium hydroxide or potassium hydroxide), *tert*-butoxycarbonyl or alkylsilyl (trimethylsilyl) may be eliminated by treatment with a suitable acid (hydrochloric, sulfuric, phosphoric or trifluoroacetic acid), whereas arylmethoxycarbonyl group (benzyloxycarbonyl) may be eliminated by hydrogenation using a catalyst such as palladium on carbon.

Salts of the compounds of the formula I may be prepared by generally known processes such as e.g. by reacting the compounds of the formula I with a corresponding base or acid in an appropriate solvent or solvent mixture e.g. ethers (diethylether) or alcohols (ethanol, propanol or isopropanol).

Another object of the present invention concerns the use of the present compounds in the therapy of inflammatory diseases and conditions, especially of all diseases and conditions induced by excessive TNF- α and IL-1 production.

The inhibitors of production of cytokins or inflammation mediators, which are the object of the present invention, or pharmacologically acceptable salts thereof may be used in the production of drugs for the treatment and prophylaxis of any pathological condition or disease induced by excessive unregulated production of cytokins or inflammation mediators, which drugs should contain an effective dose of said inhibitors. The present invention more specifically relates to an effective dose of TNF- α inhibitor, which may be determined by usual methods.

Further, the present invention relates to a pharmaceutical formulation containing an effective non-toxic dosis of the present compounds as well as pharmaceutically acceptable carriers or solvents.

The preparation of pharmaceutical formulations may include blending, granulating, tableting and dissolving ingredients. Chemical carriers may be solid or liquid. Solid carriers may be lactose, sucrose, talcum, gelatine, agar, pectin, magnesium stearate, fatty acids etc. Liquid carriers may be syrups, oils such as olive oil, sunflower oil or soya bean oil, water etc. Similarly, the carrier may also contain a component for a sustained release of the active component such as e.g. glyceryl monostearate or glyceryl distearate. Various forms of pharmaceutical formulations may be used. Thus, if a solid carrier is used, these forms may be tablets, hard gelatine capsules, powder or granules that may be administered in capsules per os. The amount of the solid carrier may vary, but it is mainly from 25 mg to 1 g. If a liquid carrier is used, the formulation would be in the form of a syrup, emulsion, soft gelatine capsules, sterile injectable liquids such as ampoules or non-aqueous liquid suspensions.

Compounds according to the present invention may be applied per os, parenterally, locally, intranasally, intrarectally and intravaginally. The parenteral route herein means intravenous, intramuscular and subcutaneous applications. Appropriate formulations of the present compounds may be used in the prophylaxis as well as in the treatment of inflammatory diseases induced by an excessive unregulated production of cytokins or inflammation mediators, primarily TNF- α . They comprise e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic pathological conditions and diseases, eczemas, psoriasis and other inflammatory skin conditions, inflammatory eye diseases, Crohn's disease, ulcerative colitis and asthma.

The inhibitory action of the present compounds upon TNF- α and IL-1 production was determined by the following *in vitro* and *in vivo* experiments:

Determination of TNF- α and IL-1 secretion in human peripheral blood mononuclear cells *in vitro*

Human peripheral blood mononuclear cells (PBMC) were prepared from heparinized whole blood after separating PBMC on Ficoll-PaqueTMPlus (Amersham-Pharmacia). To determine the TNF- α level, $3.5\text{--}5 \times 10^4$ cells were cultivated in a total volume of 200 μ l for 18 to 24 hours on microtitre plates with a flat bottom (96 wells, Falcon) in RPMI 1640 medium, into which there were added 10% FBS (Fetal Bovine Serum, Biowhittaker) previously inactivated at 54°C/30 min, 100 units/ml of penicillin, 100 mg/ml of streptomycin and 20 mM HEPES (GIBCO). The cells were incubated at 37°C in an atmosphere with 5% CO₂ and 90% humidity. In a negative control the cells were cultivated only in the medium (NC), whereas in a positive control TNF- α secretion was triggered by adding 1 ng/ml of lipopolysaccharides (LPS, *E. coli* serotype 0111:B4, SIGMA) (PC). The effect of the tested substances upon TNF- α secretion was investigated after adding them into cultures of cells stimulated by LPS (TS). The TNF- α level in the cell supernatant was determined by ELISA procedure according to the suggestions of the producer (R&D Systems). The test sensitivity was

<3pg/ml TNF- α . The IL-1 level was determined in an assay under the same conditions and with the same number of cells and the same concentration of stimulus by ELISA procedure (R&D Systems). The percentage of inhibition of TNF- α or IL-1 production was calculated by the equation:

$$\% \text{ inhibition} = [1 - (\text{TS-NC})/(\text{PC-NC})] * 100.$$

The IC₅₀ value was defined as the substance concentration, at which 50% of TNF- α production were inhibited.

Compounds showing IC₅₀ with 20 μ M or lower concentrations are active.

Determination of TNF- α and IL-1 secretion in mouse peritoneal macrophages *in vitro*

In order to obtain peritoneal macrophages, Balb/C mouse strain males, age 8 to 12 weeks, were injected i.p. with 300 μ g of zymosan (SIGMA) dissolved in a phosphate buffer (PBS) in a total volume of 0.1 ml/mouse. After 24 hours the mice were euthanized according to the Laboratory Animal Welfare Act. The peritoneal cavity was washed with a sterile physiological solution (5 ml). The obtained peritoneal macrophages were washed twice with a sterile physiological solution and, after the last centrifugation (350 g/10 min), resuspended in RPMI 1640, into which 10% of FBS were added. In order to determine TNF- α secretion, 5×10^4 cells/well were cultivated in a total volume of 200 μ l for 18 to 24 hours on microtitre plates with a flat bottom (96 wells, Falcon) in RPMI 1640 medium, into which 10% FBS (Fetal Bovine Serum, Biowhittaker) inactivated by heat, 100 units/ml of penicillin, 100 mg/ml of streptomycin, 20 mM HEPES and 50 μ M 2-mercaptoethanol (all of GIBCO) were added. The cells were incubated at 37°C in an atmosphere with 5% CO₂ and 90% humidity. In a negative control the cells were cultivated only in a medium (NC),

whereas in a positive control the TNF- α secretion was triggered by adding 10 ng/ml of lipopolysaccharides (LPS, *E. coli* serotype 0111:B4, SIGMA) (PC). The effect of the substances upon the TNF- α secretion was investigated after adding them into cultures of cells stimulated with LPS (TS). The TNF- α level in the cell supernatant was determined by ELISA procedure specific for TNF- α or IL-1 (R&D Systems, Biosource). The percentage of inhibition of TNF- α or IL-1 production was calculated by the equation:

$$\% \text{ inhibition} = [1 - (\text{TS-NC})/(\text{PC-NC})] * 100.$$

The IC₅₀ value was defined as the substance concentration, at which 50% of TNF- α production were inhibited.

Compounds showing IC₅₀ 10 μ M or less are active.

***In vivo* model of LPS-induced excessive TNF- α or IL-1 secretion in mice**

TNF- α or IL-1 secretion in mice was induced according to the already disclosed method (Badger AM et al., *J. Pharmac. Env. Therap.*, 1996, 279:1453-1461). Balb/C males, age 8 to 12 weeks, in groups of 6 to 10 animals were used. The animals were treated p.o. either with a solvent only (in negative and in positive controls) or with solutions of substances 30 minutes prior to i.p. treatment with LPS (*E. coli* serotype 0111:B4, Sigma) in a dosis of 1-25 μ g/animal. Two hours later the animals were euthanized by means of i.p. Roumpun (Bayer) and Ketanest (Parke-Davis) injection. A blood sample of each animal was taken into a Vacutainer tube (Becton Dickinson) and the plasma was separated according to the producer's instructions. The TNF- α level in the plasma was determined by ELISA procedure (Biosource, R&D Systems) according to the producer's instructions. The test sensitivity was <3pg/ml TNF- α . The

IL-1 level was determined by ELISA procedure (R&D Systems). The percentage of inhibition of TNF- α or IL-1 production was calculated by the equation:

$$\% \text{ inhibition} = [1 - (\text{TS-NC})/(\text{PC-NC})] * 100.$$

Active are the compounds showing 30% or more inhibition of TNF- α production at a dosis of 10 mg/kg.

Writhing assay for analgetic activity

In this assay pain is induced by the injection of an irritant, most frequently acetic acid, into the peritoneal cavity of mice. Animals react with characteristic writhings, which has given the name of the assay (Collier HOJ et al., *Pharmac. Chemother.*, 1968, 32:295-310; Fukawa K et al., *J. Pharmacol. Meth.*, 1980, 4:251-259; Schweizer A et al., *Agents Actions*, 1988, 23:29-31). The assay is convenient for the determination of analgetic activity of compounds. Procedure: male Balb/C mice (Charles River, Italy), age 8 to 12 weeks, were used. A control group received methyl cellulose p.o. 30 minutes prior to i.p. application of acetic acid in a concentration of 0.6%, whereas test groups received standard (acetylsalicylic acid) or test substances in methyl cellulose p.o. 30 minutes prior to i.p. application of 0.6% acetic acid (volume 0.1 ml/10 g). The mice were placed individually under glass funnels and the number of writhings was registered for 20 minutes for each animal. The percentage of writhing inhibition was calculated according to the equation:

$$\% \text{ inhibition} = (\text{mean value of number of writhings in the control group} - \text{number of writhings in the test group}) / \text{number of writhings in the control group} * 100.$$

Active are the compounds showing such analgetic activity as acetylsalicylic acid or better.

***In vivo* model of LPS-induced shock in mice**

Male Balb/C mice (Charles River, Italy), age 8 to 12 weeks, were used. LPS isolated from *Serratia marcescens* (Sigma, L-6136) was diluted in sterile physiological solution. The first LPS injection was administered intradermally in a dose of 4 µg/mouse. 18 to 24 hours later, LPS was administered i.v. in a dose of 90-200 µg/mouse. A control group received two LPS injections as disclosed above. The test groups received substances p.o. half an hour prior to each LPS application. Survival after 24 hours was observed.

Active are the substances at which the survival at a dose of 30 mg/kg was 40% or more.

Compounds from Examples (19 and 20) show activity in at least two investigated assays though these results only represent an illustration of the biological activity of the compounds and should not limit the invention in any way.

Preparation Methods With Examples

The present invention is illustrated by the following Examples which are in no way a limitation thereof.

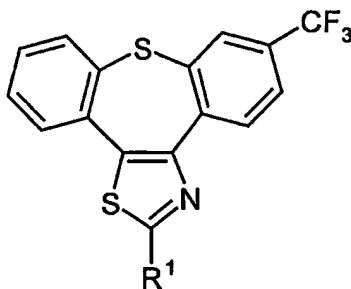
Example 1***2-Phenyl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene (1; Table 1)***

A solution of *11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]thiepin-10-one* (0.3 mmole) and thiobenzamide (0.6 mmole) in N,N-dimethylformamide (4 ml) was heated for 6 hours at the temperature of 80 °C. The solvent was evaporated at reduced

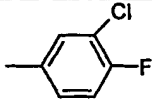
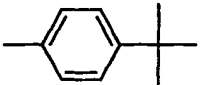
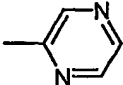
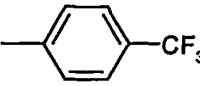
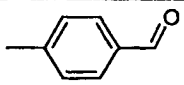
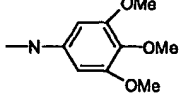
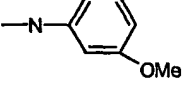
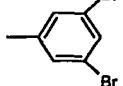
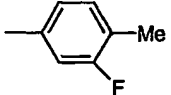
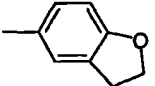
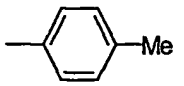
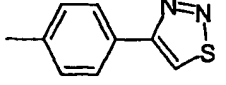
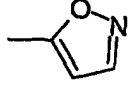
pressure to a dry residue and the crude product was purified by extraction on a solid phase (reverse-phase column RP-C18).

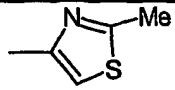
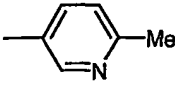
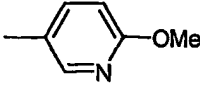
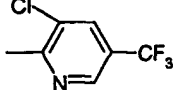
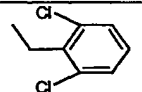
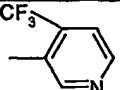
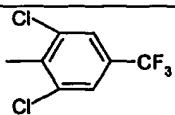
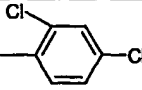
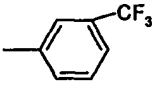
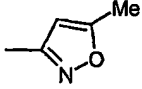
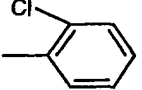
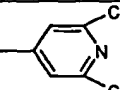
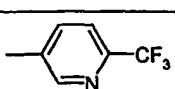
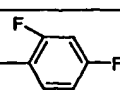
According to the above process, by a reaction of *11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]thiepin-10-one* and the corresponding thioamide, corresponding azulenes were obtained (Table 1, compounds 2-33).

Table 1



Comp.	R ¹	Mol. formula	MS: <i>m/z</i> MH ⁺
1		C ₂₂ H ₁₂ F ₃ NS ₂	412.8
2		C ₂₂ H ₁₂ ClF ₃ NS ₂	446.7
3		C ₂₁ H ₁₁ F ₃ N ₂ S ₂	413.7
4		C ₂₁ H ₁₁ F ₃ N ₂ S ₂	413.8
5		C ₂₀ H ₁₀ F ₃ NS ₃	418.7
6		C ₂₆ H ₁₅ F ₃ N ₂ S ₂	477.8

7		$C_{22}H_{10}ClF_4S_2$	464.1
8		$C_{26}H_{20}F_3NS_2$	468.7
9		$C_{20}H_{10}F_3N_3S_2$	415.3
10		$C_{23}H_{11}F_6NS_2$	480.8
11		$C_{23}H_{12}F_3NOS_2$	440.2
12		$C_{25}H_{19}F_3N_2O_3S_2$	517.1
13		$C_{23}H_{15}F_3N_2OS_2$	457.8
14		$C_{22}H_{10}Br_2F_3NS_2$	567.9
15		$C_{23}H_{13}F_4NS_2$	444.1
16		$C_{24}H_{14}F_3NOS_2$	454.1
17		$C_{23}H_{14}F_3NS_2$	426.1
18		$C_{24}H_{12}F_3N_3S_3$	496.0
19		$C_{19}H_9F_3N_2OS_2$	403.1

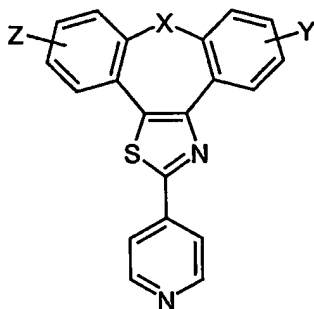
20		$C_{20}H_{11}F_3N_2S_3$	433.0
21		$C_{22}H_{13}F_3N_2S_2$	427.1
22		$C_{22}H_{13}F_3N_2OS_2$	443.1
23		$C_{22}H_9ClF_6N_2S_2$	515.1
24		$C_{23}H_{12}Cl_2F_3NS_2$	494.2
25		$C_{22}H_{10}F_6N_2S_2$	480.8
26		$C_{23}H_9Cl_2F_6NS_2$	548.2
27		$C_{22}H_{10}Cl_2F_3NS_2$	480.0
28		$C_{23}H_{11}F_6NS_2$	480.1
29		$C_{20}H_{11}F_3N_2OS_2$	417.1
30		$C_{22}H_{11}ClF_3NS_2$	446.0
31		$C_{21}H_9Cl_2F_3N_2S_2$	481.2
32		$C_{22}H_{10}F_6N_2S_2$	481.3
33		$C_{22}H_{10}F_5NS_2$	448.1

Example 2*2-Pyridine-4-yl-6-trifluoromethyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene*
(34; Table 2)

A solution of *11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]oxepin-10-one* (0.4 mmole) and pyridinium bromide perbromide (0.45 mmole) in toluene (5 ml) was stirred at room temperature for 4 hours. Then K_2CO_3 (50 mg) was added to the reaction mixture. The reaction mixture was stirred for further 10 minutes and filtered. The solvent was evaporated at reduced pressure to a dry residue. To the obtained *11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]oxepin-10-one* thioisonicotinamide (0.5 mmole) dissolved in N,N-dimethylformamide (4 ml) was added. The reaction mixture was heated at 80°C for 6 hours. The solvent was evaporated at reduced pressure to a dry residue and a crude product was purified by extraction on a solid phase (reverse-phase column RP-C18).

According to the above process, by a reaction of thioisonicotinamide and the corresponding bromoketone, corresponding azulenes were obtained (Table 2, compounds 35-49).

Table 2



Comp.	X	Y	Mol. formula	MS:(m/z) MH ⁺
34	O	6-CF ₃	C ₂₁ H ₁₁ F ₃ N ₂ OS	397.1
35	S	5-Cl; 6-Cl	C ₂₀ H ₁₀ Cl ₂ N ₂ S ₂	412.8
36	CH ₂	H	C ₂₁ H ₁₄ N ₂ S	327.1
37	S	5-OMe	C ₂₁ H ₁₄ N ₂ OS ₂	375.0
38	S	5-F	C ₂₀ H ₁₁ FN ₂ S ₂	363.1
39	S	7-Cl	C ₂₀ H ₁₁ ClN ₂ S ₂	379.0
40	S	6-Cl	C ₂₀ H ₁₁ ClN ₂ S ₂	379.0
41	S	7-Br	C ₂₀ H ₁₁ BrN ₂ S ₂	345.1
42	S	5-Br	C ₂₀ H ₁₁ BrN ₂ S ₂	423.0
43	S	5-F; 7-Cl	C ₂₀ H ₁₀ ClFN ₂ S ₂	397.0
44	S	5-Me	C ₂₁ H ₁₄ N ₂ S ₂	359.1
45	S	7-Me	C ₂₁ H ₁₄ N ₂ S ₂	359.1
46	S	5-Cl	C ₂₀ H ₁₁ ClN ₂ S ₂	379.1
47	S	6-Me	C ₂₁ H ₁₄ N ₂ S ₂	359.1
48	S	5-F; 6-Cl	C ₂₀ H ₁₀ ClFN ₂ S ₂	397.1
49	NCOMe	H	C ₂₂ H ₁₅ N ₃ OS	369.9

In all examples given in the Table 2, Z = H.

Example 3*8-Oxa-1-thia-3-aza-dibenzo[e,h]azulene (50; Table 3)*

To a solution of phosphorous (V) sulfide (6.54 mmoles) in formamide (102 mmoles; 4.08 ml), a toluene solution (8.2 ml) of *11-bromo-11H-dibenzo[b,f]oxepin-10-one* (4.60 mmoles) was added. The reaction mixture was heated under stirring and refluxing for 4 hours. Then the reaction mixture was neutralized with 10 % sodium hydroxide and extracted with chloroform. After purification by chromatography on a silica gel column, a crystalline product was isolated.

According to the above process, starting from the compounds:

11-bromo-8-fluoro-11H-dibenzo[b,f]oxepin-10-one;

11-bromo-8-chloro-11H-dibenzo[b,f]oxepin-10-one;

11-bromo-11H-dibenzo[b,f]thiepin-10-one

there were prepared:

5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;

5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;

1,8-dithia-3-aza-dibenzo[e,h]azulene,

(Table 3, compounds 51-53).

Example 4*5-Fluoro-2-methyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene (54; Table 3)*

To a solution of *11-bromo-8-fluoro-11H-dibenzo[b,f]oxepin-10-one* (2.34 mmoles) in dry N,N-dimethylformamide (12 ml), thioacetamide (2.8 mmoles) was added. The reaction mixture was heated under stirring at 90°C for 3 hours. Then the solvent was evaporated under reduced pressure and the remaining oily product was dissolved in

ethyl acetate and water. After extraction the organic layers were washed with a saturated aqueous NaHCO_3 solution, water and a saturated aqueous sodium chloride solution. After purification by chromatography on a silica gel column, a crystalline product was isolated.

According to the above process, starting from the compounds:

11-bromo-8-chloro-11H-dibenzo[b,f]oxepin-10-one;
11-bromo-7-chloro-11H-dibenzo[b,f]thiepin-10-one;
11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]thiepin-10-one;
7,11-dibromo-11H-dibenzo[b,f]thiepin-10-one;
8,11-dibromo-11H-dibenzo[b,f]thiepin-10-one;
11-bromo-8-chloro-11H-dibenzo[b,f]thiepin-10-one;
11-bromo-11H-dibenzo[b,f]thiepin-10-one;
11-bromo-11H-dibenzo[b,f]oxepin-10-one

there were prepared:

5-chloro-2-methyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;
6-chloro-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-methyl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
6-bromo-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-bromo-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-chloro-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-methyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene,
(Table 3, compounds 55-62).

Example 5

(6-Chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-acetonitrile (63; Table 3)

To a solution of *11-bromo-7-chloro-11H-dibenzo[b,f]thiepin-10-one* (3.75 mmoles) in absolute ethanol (19 ml), 2-cyanothioacetamide (5.63 mmoles) was added. The reaction mixture was heated under stirring and refluxing for 8 hours. Then the solvent was evaporated under reduced pressure and the remaining dry residue was dissolved in water and ethyl acetate. After extraction the organic layers were washed with a saturated aqueous NaHCO₃ solution, water and a saturated aqueous sodium chloride solution. After purification by chromatography on a silica gel column a crystalline product was isolated.

Example 6

6-Trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-carboxylic acid ethyl ester (70; Table 3)

To a solution of *11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]thiepin-10-one* (1.37 mmoles) in dry N,N-dimethylformamide (7 ml), ethyl thiooxamate (1.5 mmoles) was added. The reaction mixture was heated under stirring at 80°C for 3 hours. Then the solvent was evaporated under reduced pressure and the remaining oily product was dissolved in ethyl acetate and water. After extraction the organic layer was washed with a saturated aqueous NaHCO₃ solution, water and a saturated aqueous sodium chloride solution. After purification by chromatography on a silica gel column a crystalline product was isolated.

According to the above process, starting from

11-bromo-8-fluoro-11H-dibenzo[b,f]thiepin-10-one

there was prepared

5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-carboxylic acid ethyl ester
(71; Table 3).

Example 7

8-Oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde (64; Table 3)

To a solution of the compound **50** (1.99 mmoles) in dry tetrahydrofuran (5 ml), cooled to -78 °C, *n*-BuLi (5.77 mmoles) was added. After 15 minutes N,N-dimethylformamide (4.98 mmoles; 0.38 ml) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 1 hour, then water was added and it was extracted with ethyl acetate. The combined organic extracts were evaporated under reduced pressure and the remaining dry residue was purified by chromatography on a silica gel column.

According to the above process, starting from the compounds **51-53**, there were prepared the aldehydes:

5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;

5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;

1,8-dithia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;

(compounds **65-67**; Table 3).

Example 8

(6-Chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-acetic acid ethyl ester
(69; Table 3)

To a solution of the compound **63** (0.53 mmole) in ethanol (2 ml) concentrated sulfuric acid (0.5 ml) was added dropwise under stirring. The reaction mixture was heated under refluxing for 4 hours and then cooled to room temperature and poured

into water (5 ml). The reaction mixture was extracted with ethyl acetate. The combined organic extracts were evaporated under reduced pressure, whereat an oily product remained.

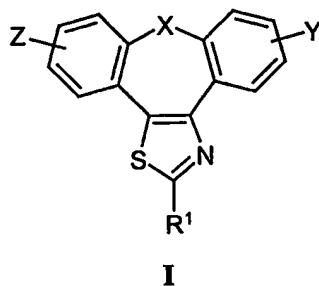
Example 9

5-Fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl-acetic acid methyl ester
(72; Table 3)

To a solution of the compound **54** (0.21 mmole) in acetic acid (5 ml), lead (IV) acetate was added under stirring. The reaction mixture was heated under refluxing for 8 hours. Then acetic acid was evaporated under reduced pressure and the remaining dry residue was dissolved in water and extracted with ethyl acetate. The combined extracts were washed with water and a saturated aqueous sodium chloride solution and evaporated under reduced pressure. After purification by chromatography on a silica gel column a crystalline product was isolated.

According to the above process, starting from the compound **55**, there was prepared *5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl-acetic acid methyl ester* (73; Table 3).

Table 3



Comp.	X	Y	R ¹	MS(<i>m/z</i>) MH ⁺	¹ H NMR (ppm, CDCl ₃)
50	O	H	H	251.9	7.16-7.98 (m, 8H); 8.86 (s, 1H)
51	O	5-F	H	270.0	7.01-7.70 (m, 7H); 8.96 (s, 1H)
52	O	5-Cl	H	-	7.22-7.99 (m, 7H); 8.94 (s, 1H)
53	S	H	H	268.0	7.02-8.98 (m, 8H); 9.13 (s, 1H)
54	O	5-F	CH ₃	-	2.84 (s, 3H); 7.20-8.33 (m, 7H)
55	O	5-Cl	CH ₃	-	2.89 (s, 3H); 7.20-8.33 (m, 7H)
56	S	6-Cl	CH ₃	316.2	-
57	S	6-CF ₃	CH ₃	350.0	-
58	S	6-Br	CH ₃	362.2	-
59	S	5-Br	CH ₃	361.0	-
60	S	5-Cl	CH ₃	316.0	-
61	S	H	CH ₃	282.2	-
62	O	H	CH ₃	-	7.18-8.98 (m, 8H); 2.84 (s, 3H)
63	S	6-Cl	CH ₂ CN	341.2	3.45 (s, 2H); 7.26-7.82 (m, 7H)
64	O	H	CHO	280.3	6.99-7.99 (m, 8H); 10.05 (s, 1H)
65	O	5-F	CHO	-	7.20-7.99 (m, 7H); 10.05 (s, 1H)
66	O	5-Cl	CHO	-	7.14-7.99 (m, 7H); 9.97 (s, 1H)
67	S	H	CHO	296.1	7.21-7.96 (m, 8H); 10.07 (s, 1H)
68	S	6-Cl	CH=CH ₂	328.1	-
69	S	6-Cl	CH ₂ CO ₂ C ₂ H ₅	388.1	-

70	S	6-CF ₃	CO ₂ C ₂ H ₅	407.9	-
71	S	5-F	CO ₂ C ₂ H ₅	357.9	-
72	O	5-F	CH ₂ OCOCH ₃	342.0	-
73	O	5-Cl	CH ₂ OCOCH ₃	358.0	-

In all Examples given in the Table 3, Z = H.

Example 10

(8-Oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol (74; Table 4)

To a solution of the compound 64 (0.60 mmole) in methanol (10 ml), NaBH₄ (0.90 mmole) was added under stirring at room temperature. The reaction mixture was stirred for 15 minutes. After the complete quantity of the aldehyde had reacted, the reaction mixture was neutralized with acetic acid and the solvent was evaporated under reduced pressure. The obtained dry residue was dissolved in a saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The organic extract was washed with water and a saturated aqueous sodium chloride solution. The solvent was evaporated under reduced pressure and then the crude product was recrystallized from a mixture of ethyl acetate and hexane.

According to the above process, starting from the aldehydes 65-67, there were prepared the alcohols:

(5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;

(5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;

(1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol

(Table 4, compounds 75-77).

Example 11

2-(6-Chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-ethanol (78; Table 4)

To a suspension of LiAlH_4 in dry ether (2 mmoles / 5 ml of dry ether), an ether solution of the ester **69** (1 mmol / 5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 hours. After the complete quantity of the ester had reacted, the excess of LiAlH_4 was decomposed by the addition of diethyl ether and water. The formed white precipitate was filtered off and, after drying on anhydrous sodium sulfate, the filtrate was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column.

Example 12

(6-Trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol (79; Table 4)

To a solution of the compound **70** (0.60 mmole) in methanol (10 ml), NaBH_4 (0.90 mmole) was added under stirring at room temperature. The reaction mixture was stirred for 15 minutes. After the complete quantity of the ester had reacted, the reaction mixture was neutralized with acetic acid and the solvent was evaporated under reduced pressure. To the obtained dry residue a saturated aqueous NaHCO_3 solution was added and it was extracted with ethyl acetate. The organic extract was washed with water and a saturated aqueous sodium chloride solution. The solvent was evaporated under reduced pressure and the crude product was recrystallized from a mixture of ethyl acetate and hexane and a pure product was obtained.

According to the above process, starting from the ester **71**, there was prepared *(5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol* (80; Table 4).

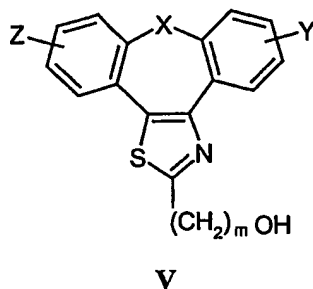
Example 13

(5-Fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol (75; Table 4)

To a solution of the ester 72 (1 mmole) in ethanol (36 ml), potassium hydroxide (2.5 mmoles) and water (4 ml) were added. The reaction mixture was stirred and heated under refluxing for 1 hour. After the complete quantity of the ester had reacted, ethanol was evaporated under reduced pressure. The obtained dry residue was dissolved in water and extracted with ethyl acetate. The organic extracts were washed with a saturated aqueous NaHCO₃ solution, water and a saturated aqueous sodium chloride solution. The obtained dry residue was purified by chromatography on a silica gel column.

According to the above process, starting from the ester 73, there was prepared the alcohol, *(5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol* (76; Table 4).

Table 4



Comp.	m	X	Y	MS (m/z) MH ⁺	¹ H NMR (ppm, CDCl ₃)
74	1	O	H	282.1	5.06 (s, 2H), 7.17-7.92 (m, 8H)
75	1	O	5-F	297.9	5.12 (s, 2H), 7.07-7.68 (m, 7H)
76	1	O	5-Cl	314.0	-
77	1	S	H	298.6	-
78	2	S	6-Cl	344.0	-
79	1	S	6-CF ₃	366.0	-
80	1	S	5-F	315.9	-

In all Examples given in the Table 4, Z = H.

Example 14

- a) *Dimethyl-[2-(8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-amine*
(I; X = O, Y = Z = H, R¹ = (CH₃)₂N(CH₂)₂OCH₂)

To a solution of 2-dimethylaminoethylchloride-hydrochloride (14 mmoles) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.44 mmole) and a

solution of the alcohol **74** (1 mmole) in toluene (3 ml) were added. The reaction mixture was heated under refluxing and vigorous stirring for 4 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column an oily product was isolated.

^1H NMR (ppm, CDCl_3): 2.58 (s, 6H); 2.92-2.95 (t, 2H); 3.92-3.98 (t, 2H); 4.91 (s, 2H); 7.15-7.90 (m, 8H);
MS (m/z): 353.3 (MH^+).

b) *Dimethyl-[3-(8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-amine* (I ; $X = \text{O}$, $Y = Z = \text{H}$, $\text{R}^1 = (\text{CH}_3)_2\text{N}(\text{CH}_2)_3\text{OCH}_2$)

By reacting the alcohol **74** (1.5 mmoles) and 3-dimethylaminopropylchloride-hydrochloride (21 mmoles) an oily product was obtained.

^1H NMR (ppm, CDCl_3): 2.23 (m, 2H); 2.83-2.85 (d, 6H); 3.15-3.25 (m, 2H); 3.72-3.84 (t, 2H); 4.90 (s, 2H); 7.18-7.91 (m, 8H);
MS (m/z): 367.3 (MH^+).

c) *3-(8-Oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-amine* (I ; $X = \text{O}$, $Y = Z = \text{H}$, $\text{R}^1 = \text{H}_2\text{N}(\text{CH}_2)_3\text{OCH}_2$)

By reacting the alcohol **74** (1.5 mmol) and 3-aminopropylchloride-hydrochloride (21 mmoles) an oily product was obtained.

MS (m/z): 339.1 (MH^+).

Example 15

- a) [2-(5-Fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine (*I*; $X = O$, $Y = 5-F$, $Z = H$, $R^1 = (CH_3)_2N(CH_2)_2OCH_2$)

To a solution of 2-dimethylaminoethylchloride-hydrochloride (21 mmoles) in 50 % sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.25 g) and a solution of the alcohol 75 (1.5 mmoles) in toluene (5 ml) were added. The reaction mixture was heated under refluxing and vigorous stirring for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column an oily product was isolated.

1H NMR (ppm, $CDCl_3$): 2.67 (s, 6H); 2.92-3.03 (m, 2H); 4.02-4.10 (m, 2H); 4.91 (s, 2H); 7.02-7.59 (m, 7H);

MS (m/z): 371.3 (MH^+).

- b) [3-(5-Fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine (*I*; $X = O$, $Y = 5-F$, $Z = H$, $R^1 = (CH_3)_2N(CH_2)_3OCH_2$)

By reacting the alcohol 75 (1.5 mmoles) and 3-dimethylaminopropylchloride-hydrochloride (21 mmoles) an oily product was obtained.

MS (m/z): 385.0 (MH^+).

Example 16

- a) [2-(5-Chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine (*I*; $X = O$, $Y = 5-Cl$, $Z = H$, $R^1 = (CH_3)_2N(CH_2)_2OCH_2$)

To a solution of 2-dimethylaminoethylchloride-hydrochloride (21 mmoles) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.25 g) and a solution of the alcohol 76 (1.5 mmoles) in toluene (4 ml) were added. The reaction mixture was

heated under refluxing and vigorous stirring for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column an oily product was isolated. MS (m/z): 386.9 (MH^+).

- b) *[3-(5-Chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine* (I; $X = O$, $Y = 5-Cl$, $Z = H$, $R^1 = (CH_3)_2N(CH_2)_3OCH_2$)

By reacting the alcohol 76 (1.5 mmoles) and 3-dimethylaminopropylchloride-hydrochloride (21 mmoles) an oily product was obtained.

1H NMR (ppm, $CDCl_3$): 1.87-2.00 (m, 2H); 2.32 (s, 6H); 2.39-2.54 (t, 2H); 3.57-3.87 (t, 2H); 4.86 (s, 2H); 7.17-7.88 (m, 7H);

MS (m/z): 401.0 (MH^+).

Example 17

- a) *[2-(1,8-Dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine* (I; $X = S$, $Y = Z = H$, $R^1 = (CH_3)_2N(CH_2)_2OCH_2$)

To a solution of 2-dimethylaminoethylchloride-hydrochloride (21 mmoles) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.25 g) and a solution of the alcohol 77 (1.5 mmoles) in toluene (3 ml) were added. The reaction mixture was heated under refluxing and vigorous stirring for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column, an oily product was isolated.

MS (m/z): 369.2 (MH^+).

- b) *[3-(1,8-Dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine*
 (I; $X = S$, $Y = Z = H$, $R^1 = (CH_3)_2N(CH_2)_3OCH_2$)

By reacting the alcohol 77 (1.5 mmoles) and 3-dimethylaminopropylchloride-hydrochloride (21 mmoles) an oily product was obtained.

1H NMR (ppm, $CDCl_3$): 2.27-2.32 (m, 2H); 2.83-2.84 (d, 6H); 3.15-3.25 (t, 2H); 3.83-3.87 (t, 2H); 4.99 (s, 2H); 7.08-7.55 (m, 8H);

MS (m/z): 383.1 (MH^+).

Example 18

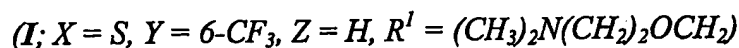
{3-[2-(6-Chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-ethoxy]-propyl}-dimethylamine (I; $X = S$, $Y = 6-Cl$, $Z = H$, $R^1 = (CH_3)_2N(CH_2)_3O(CH_2)_2$)

6-Chloro-2-vinyl-1,8-dithia-3-aza-dibenzo[e,h]azulene
 (I; $X = S$, $Y = 6-Cl$, $Z = H$, $R^1 = (CH_2 = CH)$)

To a solution of 3-dimethylaminopropylchloride-hydrochloride (14 mmoles) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.25 g) and a solution of the alcohol 78 (1 mmol) in toluene (2 ml) were added. The reaction mixture was heated under refluxing and vigorous stirring for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column an oily product, *{3-[2-(6-chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-ethoxy]-propyl}-dimethylamine*; MS (m/z): 431.3 (MH^+), and crystalline *6-chloro-2-vinyl-1,8-dithia-3-aza-dibenzo[e,h]azulene* (68; Table 3); were isolated.

Example 19

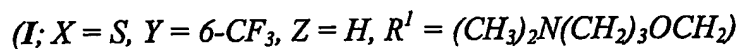
- a) *Dimethyl-[2-(6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-amine*



To a solution of 2-dimethylaminoethylchloride-hydrochloride (12 mmole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.044 mmole) and a solution of the alcohol 79 (1.1 mmole) in toluene (4 ml) were added. The reaction mixture was heated under refluxing and vigorous stirring for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column, an oily product was isolated.

MS (m/z): 437.1 (MH^+).

- b) *Dimethyl-[3-(6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-amine*



By reacting the alcohol 79 (0.84 mmole) and 3-dimethylaminopropylchloride-hydrochloride (0.019 mole) an oily product was obtained.

MS (m/z): 451 (MH^+).

Example 20

- a) *[2-(5-Fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine* ($I; X = S, Y = 5-F, Z = H, R^I = (CH_3)_2N(CH_2)_2OCH_2$)

To a solution of 2-dimethylaminoethylchloride-hydrochloride (12 mmole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.65 mmole) and a

solution of the alcohol **80** (1.1 mmole) in toluene (5 ml) were added. The reaction mixture was heated under vigorous stirring and refluxing for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by chromatography on a silica gel column, an oily product was isolated.

MS (m/z): 387.1 (MH^+).

b) *[3-(5-Fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine (I; X = S, Y = 5-F, Z = H, R' = (CH₃)₂N(CH₂)₃OCH₂)*

By reacting the alcohol **80** (0.84 mmole) and 3-dimethylaminopropylchloride-hydrochloride (19 mmoles) an oily product was obtained.

MS (m/z): 401.0 (MH^+).

Preparation of Starting Compounds

Preparation of α -bromoketones

11-Bromo-11H-dibenzo[b,f]oxepin-10-one (III; X = O, Y = Z = H)

To a solution of *11H-dibenzo[b,f]oxepin-10-one* (6.8 mmoles) in 6 ml of acetic acid, previously heated to 55-60 °C, a solution of bromine (7.5 mmoles, 0.382 ml) in 3 ml of acetic acid was added dropwise under stirring. The reaction mixture was stirred at the temperature of 60 °C for 1.5 hours and then purged by a flow of argon, whereby hydrogen bromide was formed. After cooling to room temperature, the reaction mixture was poured into water and extracted with dichloromethane. The obtained precipitate was recrystallized from ethanol and the obtained crystals were filtered off.

According to the above process, starting from:

8-fluoro-11H-dibenzo[b,f]oxepin-10-one;

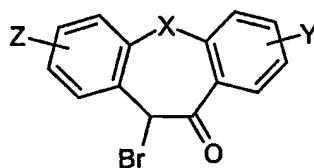
8-chloro-11H-dibenzo[b,f]oxepin-10-one;
 11H-dibenzo[b,f]thiepin-10-one;
 7-chloro-11H-dibenzo[b,f]thiepin-10-one;
 7-trifluoromethyl-11H-dibenzo[b,f]thiepin-10-one;
 8-fluoro-11H-dibenzo[b,f]thiepin-10-one;
 8-chloro-11H-dibenzo[b,f]thiepin-10-one;
 7-bromo-11H-dibenzo[b,f]thiepin-10-one;
 8-bromo-11H-dibenzo[b,f]thiepin-10-one,
 7,8-dichloro-11H-dibenzo[b,f]thiepin-10-one;
 8-methoxy-11H-dibenzo[b,f]thiepin-10-one

there were prepared the compounds:

11-bromo-8-fluoro-11H-dibenzo[b,f]oxepin-10-one (**III**; $X = O$, $Y = 8-F$, $Z = H$);
 11-bromo-8-chloro-11H-dibenzo[b,f]oxepin-10-one (**III**; $X = O$, $Y = 8-Cl$, $Z = H$);
 11-bromo-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = Z = H$);
 11-bromo-7-chloro-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 7-Cl$, $Z = H$);
 11-bromo-7-trifluoromethyl-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 7-CF_3$,
 $Z = H$);
 11-bromo-8-fluoro-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 8-F$, $Z = H$);
 11-bromo-8-chloro-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 8-Cl$, $Z = H$);
 7,11-dibromo-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 7-Br$, $Z = H$);
 8,11-dibromo-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = O$, $Y = 8-Br$, $Z = H$);
 11-bromo-7,8-dichloro-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 7-Cl$ and
 8-Cl, $Z = H$);
 11-bromo-8-methoxy-11H-dibenzo[b,f]thiepin-10-one (**III**; $X = S$, $Y = 5-OCH_3$,
 $Z = H$).

The characteristics of the obtained products of the formula **III** are shown in the Table 5.

Table 5



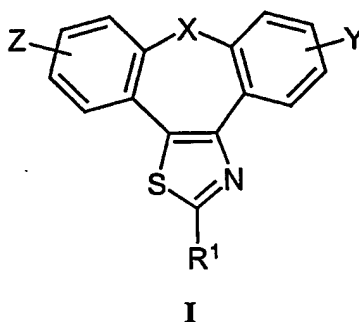
III

X	Y	¹ H NMR (ppm, CDCl ₃)
O	H	5.62 (s, 1H); 7.21-8.19 (m, 8H)
O	8-F	5.61 (s, 1H); 7.16-8.19 (m, 7H)
O	8-Cl	5.59 (s, 1H); 7.26-8.19 (m, 7H)
S	H	6.77 (s, 1H); 7.19-8.28 (m, 8H)
S	7-Cl	6.72 (s, 1H); 7.25-8.19 (m, 7H)
S	7-CF ₃	6.71 (s, 1H); 7.24-8.35 (m, 7H)
S	8-F	6.79 (s, 1H); 7.05-7.97 (m, 7H)
S	8-Cl	6.71 (s, 1H); 7.11-8.27 (m, 7H)
S	7-Br	6.71 (s, 1H); 7.26-8.09 (m, 7H)
S	8-Br	6.71 (s, 1H); 7.27-8.36 (m, 7H)
S	7-Cl; 8-Cl	6.69 (s, 1H); 7.25-8.28 (m, 6H)
S	8-OCH ₃	3.82 (s, 3H); 6.84 (s, 1H); 7.03-7.87 (m, 7H)

In all Examples given in the Table 5, Z = H.

Claims

1. A compound of the formula I



characterized in that

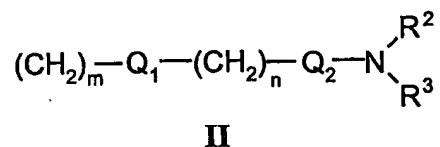
X may be CH₂ or a hetero atom such as O, S, S(=O), S(=O)₂, or NR^a, wherein R^a is hydrogen or a protecting group;

Y and Z independently from each other denote one or more identical or different substituents linked to any available carbon atom, and may be halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo-C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, trifluoromethoxy, C₁-C₄ alkanoyl, amino, amino-C₁-C₄ alkyl, N-(C₁-C₄-alkyl)amino, N,N-di(C₁-C₄-alkyl)amino, thiol, C₁-C₄ alkylthio, sulfonyl, C₁-C₄ alkylsulfonyl, sulfinyl, C₁-C₄ alkylsulfinyl, carboxy, C₁-C₄ alkoxycarbonyl, cyano, nitro;

R¹ may be hydrogen, halogen, an optionally substituted C₁-C₇ alkyl or C₂-C₇ alkenyl, C₂-C₇ alkynyl, an optionally substituted aryl or heteroaryl and a heterocycle, hydroxy, hydroxy-C₂-C₇ alkenyl, hydroxy-C₂-C₇ alkynyl, C₁-C₇ alkoxy, thiol, thio-C₂-C₇ alkenyl, thio-C₂-C₇ alkynyl, C₁-C₇ alkylthio, amino-C₂-C₇ alkenyl, amino-C₂-C₇ alkynyl, amino-C₁-C₇ alkoxy, C₁-C₇ alkanoyl, aroyl, oxo-C₁-C₇ alkyl, C₁-C₇ alkanoyloxy, carboxy, an optionally substituted (C₁-C₇ alkylloxycarbonyl or aryloxycarbonyl), carbamoyl, N-(C₁-C₇-alkyl)carbamoyl, N,N-di(C₁-C₇-alkyl)carbamoyl, cyano,

cyano-C₁-C₇ alkyl, sulfonyl, C₁-C₇ alkylsulfonyl, sulfinyl, C₁-C₇ alkylsulfinyl, nitro,

or a substituent of the formula II



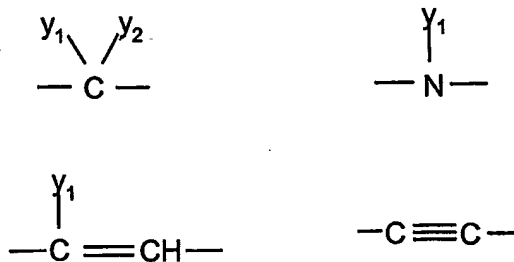
wherein

R² and R³ simultaneously or independently from each other may be hydrogen, C₁-C₄ alkyl, aryl or together with N have the meaning of an optionally substituted heterocycle or heteroaryl;

m represents an integer from 1 to 3;

n represents an integer from 0 to 3;

Q₁ and Q₂ represent, independently from each other, oxygen, sulfur or groups:



wherein the substituents

y₁ and y₂ independently from each other may be hydrogen, halogen, an optionally substituted C₁-C₄ alkyl or aryl, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkanoyl, thiol, C₁-C₄ alkylthio, sulfonyl, C₁-C₄ alkylsulfonyl, sulfinyl, C₁-C₄ alkylsulfinyl, cyano, nitro or together form carbonyl or imino group;

as well as pharmacologically acceptable salts and solvates thereof.

2. A compound according to claim 1, **characterized in that** Y and Z have the meanings of H, F, Cl, Br, CF₃, OCH₃.
3. A compound according to claim 2, **characterized in that** R¹ has the meanings of H, CH₃, CH₂CN, CHO, CH=CH₂, CH₂COOC₂H₅, COOC₂H₅, CH₂OCOCH₃.
4. A compound according to claim 1, **characterized in that** R¹ has the meanings of aryl, heteroaryl.
5. A compound according to claim 2, **characterized in that** R¹ has the meanings of (CH₂)_mOH.
6. A compound according to claim 5, **characterized in that** the symbol m has the meanings of 1 or 2.
7. A compound according to claim 2, **characterized in that** R¹ has the meanings of the formula II.
8. A compound according to claim 7, **characterized in that** m has the meanings of 1 or 2, n has the meanings of 1 or 2, Q₁ represents O, Q₂ represents CH₂, and R² and R³ represent hydrogen and methyl.
9. Selected compounds according to claim 3:
8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;
5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;
5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;

1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-chloro-2-methyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;
5-fluoro-2-methyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;
6-chloro-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-methyl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
6-bromo-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-bromo-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-chloro-2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-methyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-methyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;
(6-chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-acetonitrile;
8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;
5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;
5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;
1,8-dithia-3-aza-dibenzo[e,h]azulene-2-carbaldehyde;
6-chloro-2-vinyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
(6-chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-acetic acid ethyl ester;
6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-carboxylic acid ethyl ester;
5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-carboxylic acid ethyl ester;
5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl-acetic acid methyl ester;
5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl-acetic acid methyl ester.

10. Selected compounds according to claim 4:

2-phenyl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-(4-chloro-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-pyridine-3-yl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-pyridine-4-yl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
2-thiophene-3-yl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(3-pyrrole-1-yl-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(3-chloro-4-fluoro-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(4-tert-butyl-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-pyrazine-2-yl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

6-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(4-[1,3]dioxolane-2-yl-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

(6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-(3,4,5-trimethoxy-phenyl)amine;

(3-methoxy-phenyl)-(6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-amine;

2-(3,5-dibromo-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(3-fluoro-4-methyl-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2,3-dihydro-benzofuran-5-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-p-tolyl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(4-[1,2,3]thiadiazole-4-yl-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-isoxazole-5-yl-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2-methyl-thiazole-4-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(6-methyl-pyridine-3-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(6-methoxy-pyridine-3-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(3-chloro-5-trifluoromethyl-pyridine-2-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2,6-dichloro-benzyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

6-trifluoromethyl-2-(4-trifluoromethyl-pyridine-3-yl)-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2,6-dichloro-4-trifluoromethyl-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2,4-dichloro-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

6-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(5-methyl-isoxazole-3-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2-chloro-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2,6-dichloro-pyridine-4-yl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

6-trifluoromethyl-2-(6-trifluoromethyl-pyridine-2-yl)-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-(2,4-difluoro-phenyl)-6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-pyridine-4-yl-6-trifluoromethyl-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene;

5,6-dichloro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

2-pyridine-4-yl-8H-1-thia-3-aza-dibenzo[e,h]azulene;

5-methoxy-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

5-fluoro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

7-chloro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

7-bromo-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

6-chloro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

5-bromo-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;

7-chloro-5-fluoro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-methyl-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
7-methyl-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
5-chloro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
6-methyl-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
6-chloro-5-fluoro-2-pyridine-4-yl-1,8-dithia-3-aza-dibenzo[e,h]azulene;
1-(2-pyridine-4-yl-1-thia-3,8-diaza-dibenzo[e,h]azulene-8-yl)-ethanone.

11. Selected compounds according to claim 6:

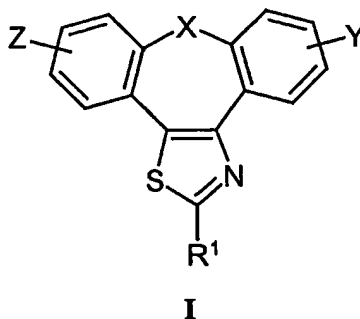
(8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;
(5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;
(5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;
(1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;
2-(6-chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-ethanol;
(6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol;
(5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-methanol.

12. Selected compounds according to claim 8:

dimethyl-[2-(8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-amine;
dimethyl-[3-(8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-amine;
3-(8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-amine;
[2-(5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine;
[3-(5-fluoro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine;
[2-(5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine;

[3-(5-chloro-8-oxa-1-thia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine;
[2-(1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine;
[3-(1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine;
{3-[2-(6-chloro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-yl)-ethoxy]-propyl}-dimethylamine;
dimethyl-[2-(6-trifluoromethyl-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-amine;
[2-(5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine;
dimethyl-[2-(5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-ethyl]-dimethylamine;
[3-(5-fluoro-1,8-dithia-3-aza-dibenzo[e,h]azulene-2-ylmethoxy)-propyl]-dimethylamine.

13. A process for the preparation of the compounds of the formula I



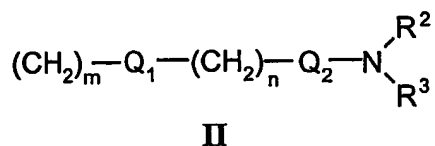
wherein

- X may be CH₂ or a hetero atom such as O, S, S(=O), S(=O)₂, or NR^a, wherein R^a is hydrogen or a protecting group;
- Y and Z independently from each other denote one or more identical or different substituents linked to any available carbon atom, and may be halogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo-C₁-C₄ alkyl, hydroxy,

C₁-C₄ alkoxy, trifluoromethoxy, C₁-C₄ alkanoyl, amino, amino-C₁-C₄ alkyl, *N*-(C₁-C₄-alkyl)amino, *N,N*-di(C₁-C₄-alkyl)amino, thiol, C₁-C₄ alkylthio, sulfonyl, C₁-C₄ alkylsulfonyl, sulfinyl, C₁-C₄ alkylsulfinyl, carboxy, C₁-C₄ alkoxycarbonyl, cyano, nitro;

R¹ may be hydrogen, halogen, an optionally substituted C₁-C₇ alkyl or C₂-C₇ alkenyl, C₂-C₇ alkynyl, an optionally substituted aryl or heteroaryl and a heterocycle, hydroxy, hydroxy-C₂-C₇ alkenyl, hydroxy-C₂-C₇ alkynyl, C₁-C₇ alkoxy, thiol, thio-C₂-C₇ alkenyl, thio-C₂-C₇ alkynyl, C₁-C₇ alkylthio, amino-C₂-C₇ alkenyl, amino-C₂-C₇ alkynyl, amino-C₁-C₇ alkoxy, C₁-C₇ alkanoyl, aroyl, oxo-C₁-C₇ alkyl, C₁-C₇ alkanoyloxy, carboxy, an optionally substituted (C₁-C₇ alkylloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C₁-C₇-alkyl)carbamoyl, *N,N*-di(C₁-C₇-alkyl)carbamoyl, cyano, cyano-C₁-C₇ alkyl, sulfonyl, C₁-C₇ alkylsulfonyl, sulfinyl, C₁-C₇ alkylsulfinyl, nitro,

or a substituent of the formula II



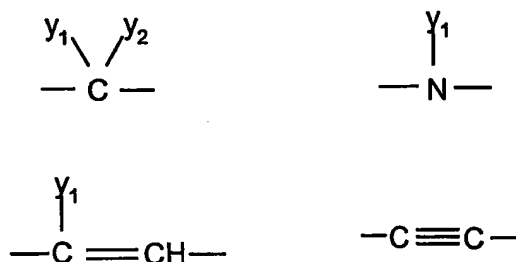
wherein

R² and R³ simultaneously or independently from each other may be hydrogen, C₁-C₄ alkyl, aryl or together with N have the meaning of an optionally substituted heterocycle or heteroaryl;

m represents an integer from 1 to 3;

n represents an integer from 0 to 3;

Q_1 and Q_2 represent, independently from each other, oxygen, sulfur or groups:



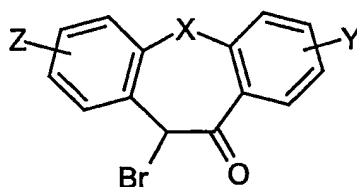
wherein the substituents

y_1 and y_2 independently from each other may be hydrogen, halogen, an optionally substituted C_1 - C_4 alkyl or aryl, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 alkanoyl, thiol, C_1 - C_4 alkylthio, sulfonyl, C_1 - C_4 alkylsulfonyl, sulfinyl, C_1 - C_4 alkylsulfinyl, cyano, nitro or together form carbonyl or imino group;

as well as of pharmacologically acceptable salts and solvates thereof,

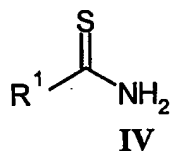
characterized in that the process of the preparation comprises:

a) a cyclization of α -bromoketones of the formula **III**:

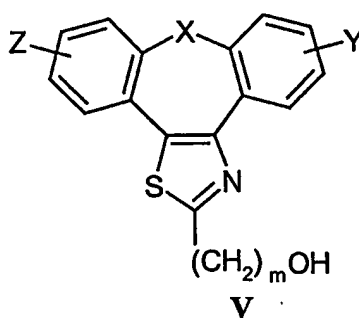


III

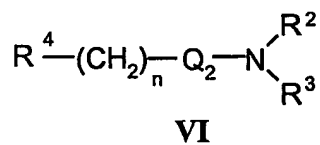
with the compounds of the formula IV:



- b) for the compounds of the formula I, wherein Q_1 has a meaning of -O-,
a reaction of alcohols of the formula V:



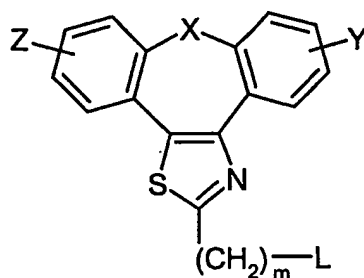
with the compounds of the formula VI:



wherein R^4 has the meaning of a leaving group;

- c) for the compounds of the formula I, wherein Q_1 has a meaning of -O-, -NH-, -S- or -C≡C-,

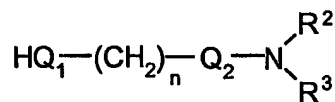
a reaction of the compounds of the formula Va:



Va

wherein L has a meaning of a leaving group,

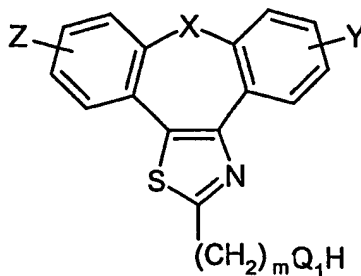
with the compounds of the formula VIa:



VIa

- d) for the compounds of the formula I, wherein Q_1 has the meaning of the heteroatom -O-, -NH- ili -S-,

a reaction of the compounds of the formula Vb:



Vb

with the compounds of the formula VI, wherein R^4 has the meaning of a leaving group;

- e) for the compounds of the formula I, wherein Q_1 has the meaning of $-C=C-$,
a reaction of the compounds of the formula Va, wherein Q_1 has the meaning of carbonyl, with phosphorous ylides.
14. Use of compounds of the formula I according to claim 3 as intermediates for the preparation of novel dibenzoazulenes of thiazole class with antiinflammatory action.
15. Use of compounds of the formula I according to claim 7 in the treatment and prophylaxis of any pathological conditions or diseases induced by excessive unregulated production of cytokins or inflammation mediators by administering a nontoxic dosis of suitable pharmaceutical preparations perorally, parenterally or locally.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/HR 03/00023

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D513/04 A61K31/55 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 87890 A (HRVA & CCARON ; MESI & CACUTE (HR); PE & SCARON (HR); MER & CACUTE) 22 November 2001 (2001-11-22) cited in the application the whole document	1-15
Y	US 4 198 421 A (CHERKOFISKY SAUL C ET AL) 15 April 1980 (1980-04-15) cited in the application the whole document	1-15
Y	US 3 711 489 A (LOMBARDINO J) 16 January 1973 (1973-01-16) cited in the application the whole document	1-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

25 July 2003

Date of mailing of the international search report

18/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No.

PCT/HR 03/00023

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0187890	A	22-11-2001	HR 20000310 A1	28-02-2002
			AU 5656001 A	26-11-2001
			BR 0111202 A	01-04-2003
			CA 2409090 A1	22-11-2001
			CZ 20024090 A3	14-05-2003
			EP 1284977 A1	26-02-2003
			WO 0187890 A1	22-11-2001
			NO 20025510 A	14-01-2003
US 4198421	A	15-04-1980	NONE	
US 3711489	A	16-01-1973	GB 1374862 A	20-11-1974
			US 3781294 A	25-12-1973